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Attorney Docket No: 402E-918102US
Client Ref: PO887C1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

#7
A.G.J
5/2/02

In re application of:

Chen, Mary

Application No.: 09/661,161

Filed: September 13, 2000

For: IMPROVING POLYPEPTIDE PRODUCTION IN ANIMAL CELL CULTURE

Examiner: Afremova, Vera

Art Unit: 1651

RESPONSE

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

In response to the Office Action dated December 13, 2001, Applicants respectfully request reconsideration of the above-identified application in view of the following remarks. The following documents are enclosed herewith:

1) A petition to extend the period for response by one month, extending the period for response through the present date;

2) Terminal Disclaimer;

3) Copy of the Reference AY: Loibner et al., Biosensors and Flow Injection Analysis in Bioprocess Control (Poster Presentation), Freising, Germany (April 8, 1992);

4) List of Pending Claims (Appendix A);

5) Transmittal;

6) Fee Transmittal

7) Receipt Acknowledgement Postcard

REMARKS

Status of the Claims.

Claims 1 and 20-25 are pending with entry of this response, no claims being cancelled or added herein.

Information Disclosure Statement.

Applicants note with appreciation the Examiner's thorough consideration of the references cited in the Information Disclosure Statement (IDS) submitted on 9-13-2000, with the exception of two references, AR and AY. According to the Examiner, no copies and/or no proper citations were provided. However, Applicants submit that proper citations were provided on the IDS submitted 9-13-2000. Applicants were not obligated to provide copies of these documents, as copies had previously been submitted to the Patent Office in an IDS (Form 1449) filed in the parent application, which was identified in the IDS submitted 9-13-2000 and was relied on for priority under § 120. The Patent Office received copies of references AR and AY in the parent application (Application No. 09/073,198), as evidenced by the Examiner's initials next to the citation for each reference in a Form 1449 attached to an Office Action dated 4/27/99 in the parent application. Accordingly, Applicants have fully complied with the requirements set forth in 37 C.F.R. §§ 1.97-1.98.

However, as a courtesy to the Examiner, Applicants have provided the Examiner with a copy of the AY reference herewith. Applicants are attempting to obtain an additional copy of the AR, but in the meantime, request that the Examiner attempt to obtain a copy of this reference from the Patent Office's file for the parent application (Application No. 09/073,198). Applicants further request Examiner to consider references AR and AY, initial the Form 1449 submitted 9-13-2000 to reflect that consideration, and forward a copy of the initialed form to the undersigned. Applicants note that, as Applicants fully complied with the requirements for disclosing art to the Patent Office, no fee is due for consideration of references AR and AY.

Obviousness-type double patenting

Claims 1 and 20-25 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 2-16 and 23-26 of U.S. Patent No. 5,856,179.

The instant application is a continuation application of U.S. Patent No. 6,180,401, which is a divisional application of U.S. Patent No. 5,856,179. The claims in the parent application, which issued as U.S. Patent No. 5,856,179, were subject to a restriction requirement and divided into four claim groups. In response to the restriction requirement, Applicants elected Claim Group II (Claims 2-17) for prosecution in the parent application and subsequently prosecuted Claim Group I

(Claim 1) in the divisional application, now U.S. Patent 6,180,401. The instant continuation application was filed to continue prosecution of independent claim 1 and dependent claims 20-25.

According to 35 U.S.C. 121, "[a] patent issuing on an application with respect to which a requirement for restriction under this section has been made . . . shall not be used as a reference either in the Patent and Trademark Office or in the courts against a divisional application . . . if the divisional application is filed before the issuance of the patent on the other application."

Claim 1 was initially prosecuted in divisional application No. 09/073,198, now U.S. Patent No. 6,180,401 which was filed as a result of the restriction requirement in the parent application. Further, the divisional application was filed prior to the issuance of the parent application. Thus, independent claim 1 of the divisional application could not have been rejected for obviousness-type double patenting over claims 2-16 of the '179 patent. Section 121 precluded such a rejection where the PTO determined that claim 1 was patentably distinct from claims 2-16 of the '179 patent. Applicants submit that this same rationale precludes the PTO from rejecting the pending claim 1 for obviousness-type double patenting over claims 2-16 of the '179 patent. In other words, this rejection is improper because the PTO has already determined that the subject matter in question is patentably distinct.

Claims 23-26 depend, directly or indirectly, from claim 2 and therefore represent subject matter that, like claims 2-16, is patentably distinct from the subject matter claimed in the present application. Therefore, Applicants respectfully request withdrawal of the nonstatutory double patenting rejection of claims 1 and 20-25 over claims in U.S. Patent No. 5,856,179.

Claims 1 and 20-25 are also rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims of U.S. Patent No. 6,180,401 [A]. This patent is commonly owned and Applicants are filing a terminal disclaimer herein in compliance with 37 CFR 1.321 (c), 37 CFR 1.130(b). Therefore, Applicants respectfully request withdrawal of the nonstatutory double patenting rejection of claims 1 and 20-25 over claims in U.S. Patent No. 6,180,401.

35 U.S.C. §112, Second Paragraph.

Claims 1 and 20-25 were rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite on various grounds. This rejection is respectfully traversed.

In particular, the Examiner found claim 1 indefinite for reciting the word "inclusive" indicating, ". . . the meaning of this limitation is unclear." Office Action, page 4. Applicants respectfully point out that under section 112, second paragraph, claims are not indefinite if one of ordinary skill in the pertinent art can understand the scope of the claim. Claim 1 recites "in the presence of glucose controlled throughout the culturing to be at a concentration between about 0.02 and about 0.2 g/L, inclusive, ..." The term "inclusive" is commonly understood to mean that it includes the limits or extremes under consideration. Therefore, one skilled in the art of animal cell culturing would understand that the recited concentration includes 0.02 g/L, as well as 0.2 g/L and all concentrations in between. Applicants submit that claim 1 is clear and definite with respect to the recited glucose concentration.

Claim 1 was found to be indefinite for reciting the phrase "thereby controlling osmolality." According to the Examiner, "it is uncertain if glucose is an osmola[l]ity regulating agent." Further, the Examiner was confused as to whether "osmola[l]ity during culturing step [is] the same as a starting osomola[l]ity of 280-330 mOsm." *Id.* Claim 1 recites " . . . by adding glucose to the cell culture as required to maintain said glucose concentration and thereby controlling osmolality of the cell culture." As one skilled in the art would readily appreciate, claim 1 clearly indicates that glucose is added to the cell culture to maintain the recited glucose concentration. Further, by practicing the invention in the manner recited in claim 1, osmolality is controlled. As indicated in Applicants' specification, one object of the invention is "to control the osmolality of an animal cell culture to be substantially maintained within a desired range, via control of the glucose . . .." Applicants' specification at page 3, lines 29-31. Applicants point out that claim 1, as written, neither excludes, nor requires, that osmolality be the same during culturing as the starting osmolality of 280-330 mOsm. Therefore, Applicants respectfully submit that claim 1 is clear and definite with respect to controlling osmolality.

The Examiner also found claim 1 and 21 to be indefinite for reciting "about." Applicants point out that the descriptive term "about" does not generally render a claim indefinite. W. L. Gore & Assocs. v. Garlock, Inc., 721 F.2d 1540, 1557, 220 USPQ 303, 316 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984). "About" is not broad or arbitrary but rather is a flexible term with a meaning similar to "approximately" or "nearly." Syntex (U.S.A.), Inc. v. Paragon Optical, Inc., 7 USPQ 2d 1001, 1038 (D. Ariz. 1987). Claim 1 recites " . . . a starting osmolality of about 280-330 mOsm in the presence of glucose controlled throughout the culturing to be at a concentration

between about 0.02 and about 0.2 g/L, inclusive . . .." Claim 21 recites ". . . initial cell density is between about $3x10^5$ and about 1.5 x 10^6 cells /mL." Applicants submit that the use of the term "about" as recited in claim 1 and claim 21 properly conveys *approximate ranges* that would be clear to one skilled in the art of animal cell culturing, particularly when viewed in light of the specification. Accordingly, claim 1 and claim 21 are clear with respect to the glucose concentration and the initial cell seed density.

According to the Examiner, claim 20 was found to be indefinite for reciting the phrase "medium contains excess amino acids" because it is unclear in excess to what amount additional amino acids are required as claimed." Claim 20 recites " . . . wherein the culture medium contains excess amino acids." Applicants respectfully submit that claim 20 is clear and definite to one skilled in the art when viewed in light of Applicants' specification.

In particular, Table 1 of Applicants' specification provides representative amino acid concentrations in ranges that are considered "excess" amino acids within the context of the present invention. Applicants' specification, Table 1, at page 11, lines 12-25. Additionally, the most preferred concentration for each of the amino acids is also listed. Applicants' specification, at page 11, lines 25-29. Moreover, Applicants submit that one skilled in the art of animal cell culturing would understand that the term "excess amino acids" indicates a level of amino acids that exceeds a level that is typically used for growing cell cultures in the manner described in the present application, i.e., fed batch culture. Applicants therefore submit that those skilled in the art would understand the term "excess amino acids." Accordingly, in light of Applicants' specification, Applicants respectfully submit that claim 20 is clear and definite with respect to excess amino acids.

As the claims are clear and definite and would be readily understood by those of skill in the art, Applicants respectfully request withdrawal of the section 112, second paragraph rejection.

35 U.S.C. §102.

Claims 1, 20-22, 24 and 25 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by Glacken et al. [IDS-AT] (hereinafter "Glacken") or JP 1-101882 [IDS-AJ] (hereinafter "JP 1") in light of Waymouth [IDS-BG] (hereinafter "Waymouth"). Waymouth is cited to establish that the methods described in Glacken or JP 1 "are reasonably expected to inherently

comprise the use of identical initial osmola[l]ity as . . . the presently claimed method." Office Action, page 6. Applicants respectfully traverse the rejection.

To establish a *prima facie* case of anticipation, the Examiner must show that each element of the claimed invention is found, expressly or under principles of inherency, in a single cited reference. See Diversitech Corp. v. Century Step, Inc., 7 U.S.P.Q. 2d 1315, 1317 (Fed. Cir. 1988). Additionally, to make out a *prima facie* case of inherency, the Examiner must provide factual and technical grounds establishing that the allegedly inherent feature necessarily flows from the teachings of the prior art. See Ex part Levy, 17 U.S.P.Q. 2d 1461, 1464 (Bd. Pat. App. & Int. 1990).

Applicants submit that the Examiner has not established a *prima facie* case of anticipation under section 102 because none of the references teach all of the elements of the present invention. Further, a *prima facie* case of inherency cannot be established because the 'allegedly inherent feature' alluded to by the Examiner, does not necessarily flow from the teachings of the cited reference.

In particular, independent claim 1 recites a "method of growing animal cells in fed batch cell culture comprising culturing the cells at a starting osmolality of about 280-330 mOsm in the presence of glucose controlled throughout the culturing to be at a concentration between about 0.02 and about 0.2g/L, inclusive, by adding glucose to the cell culture as required to maintain said glucose concentration . . .." Pending claims 20-25 incorporate all claim elements by virtue of their dependence from claim 1. None of the cited references teaches each and every element as recited in claim 1 Further, the reference cited to establish the inherency of the claimed starting osmolality, Waymouth, fails to *necessarily* teach this osmolality. The deficiencies of each of the cited references in this respect is discussed in turn below.

Glacken et al. Does Not Teach All of the Elements of the Invention

In support of the section 102(b) rejection over Glacken, the Examiner cites page 1386 col. 1, par. 3 and Figure 9, between 100 and 200 hours. Office Action, page 5. Figure 9 shows the glucose concentration in FS-4 cell cultures over time and reflects the "*adjustment of glucose set points*," the adjustment being determined by the lactic acid production rate. See Glacken, caption to Figure 9, at page 1387. At the start of the culturing the glucose set point is between about 0.4 and 0.6 mM. Then, at about hour 30, the set point is at about 0.4mM and *the set point remains at that level until about hour 70.* Glacken Figure 9, at page 1387. However, rather than teaching

"throughout"

controlling glucose concentration throughout the culturing to be at a concentration between about 0.02 and about 0.2g/L, inclusive, the cited passage describes a control scheme wherein the glucose set point was initially high and was subsequently lowered until q_L (specific lactic acid productivity) was at a desired value. See Glacken at page 1386, col. 1, par. 3. Moreover, Figure 9 shows that from hour 0 to approximately hour 70, *at approximately 6 different points in time, the glucose concentrations in the FS-4 cultures are outside of the range of between about 0.02 and about 0.2g/L, inclusive.* Glacken Figure 9, at page 1387. Therefore, Applicants submit that Glacken fails to teach controlling glucose concentration "***throughout the culturing to be at a concentration between about 0.02 and about 0.2 g/L, inclusive***," as recited in claim 1

As will be discussed herein below, Glacken is also devoid of any teaching regarding growing animal cells in fed batch cell culture at a starting osmolality of about 280-330 mOsm. Glacken describes strategies for reducing the production of lactic acid and ammonium by mammalian cells. Glacken at page 1376, col. 1, par. 1. In Glacken, human foreskin fibroblasts (FS-4) were cultured in an aerated vessel that was equipped to monitor and control pH, dissolved oxygen, and glucose levels via a computer. *Id.* at page 1377, col. 2, par. 2. *Conspicuously absent in Glacken, is any attempt to monitor, control, or determine the starting osmolality of the cell culture.* In fact, Glacken does not even indicate that the starting osmolality of the *media* is important. Furthermore, the cell culture osmolality is not determined at any time in the culturing process. Those skilled in the art would recognize that there are many factors that can influence the starting osmolality of a cell culture. Yet, Glacken fails to teach monitoring and controlling such factors in order to achieve a starting osmolality of the cell culture within the range recited in claim 1. Applicants submit, therefore, that Glacken fails to teach "***growing animal cells in fed batch cell culture comprising culturing the cells at a starting osmolality of about 280-330 mOsm***."

JP 1-101882 [IDS-AJ] Does Not Teach All of the Elements of the Invention

In support of the section 102 rejection, the Examiner cites JP-1 translation page 3 and translation page 4, par. 3. Office action, page 5-6. This passages describes a method wherein animal cells are cultured by *perfusion* system while maintaining the glucose concentration in the culture system. JP-1 translation at page 3, par 3. The Examiner noted that "[t]he perfusion system of the cited reference (translation page 4, par. 3) appears to be identical to the claimed fed-batch system . . .." Office action, page 6. Applicants respectfully submit that one skilled in the art would not share

this view, but note that this point is moot because, like Glacken, JP-1 fails to teach "culturing the cells at a starting osmolality of about 280-330 mOsm," as recited in claim 1.

JP-1 describes a method for high-density culture of animal cells. See JP-1 translation at page 2, par. 2. As with Glacken, the reference fails to teach the importance of a starting osmolality of the cell culture of about 280-330 mOsm. JP-1 also fails to determine the starting osmolality of the cell culture, and in fact, does not measure the osmolality of the cell culture at any point in the culturing process. Furthermore, JP-1 describes the use of a cultivation medium that contains various additives for example, various inorganic salts, vitamins, coenzymes, glucose, amino acids, antibiotics, growth promoting factors, etc. *Id.* at page 5, par. 1. Significantly, "[s]olutes which can be added to the culture medium so as to increase the osmolality thereof include proteins, peptides, amino acids, non-metabolized polymers, vitamins, ions, salts, sugars, metabolites, organic acids, lipids, etc. Applicants' specification at page 7, lines 29 - page 8, line 2. Therefore, since JP-1 does not measure or describe the importance of a starting osmolality of the cell culture, and since the culturing medium contains various additives that can impact osmolality, the reference clearly fails to teach "***culturing the cells at a starting osmolality of about 280-330 mOsm***," as recited in claim 1.

Waymouth Does Not Establish Inherency of Glacken or JP-1

Notably, the Examiner admits, "***the cited references do not exclusively disclose an initial osmola[l]ity of about 280 –3[2]0 mOsm for the culture media*** . . .." Office action, page 6. However, the Examiner reasons that the references "teach the use of regular animal media. And it is known that initial osmola[l]ity of regular animal media or initial osmola[l]ity of the majority of commercially available animal media is within the claimed range of 280-320 mOsm." *Id.*

Applicants respectfully point out that in order to make out a *prima facie* case of inherency, the Examiner must provide factual and technical grounds establishing that the allegedly inherent feature necessarily flows from the teachings of the prior art. See Ex part Levy, 17 U.S.P.Q. 2d 1461, 1464 (Bd. Pat. App. & Int. 1990). "Inherency . . . may not be established by probabilities or possibilities." Continental Can co. USA, Inc. v. Monsanto Co., 948 F.2d 1264, 1268-69 (Fed. Cir. 1991) (quoting In re Oelrich, 666 F.2d 578, 581 (C.C.P.A. 1981)). Further, "[a] *prima facie* case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product." M.P.E.P. 2112.01 (citing In re Best, 562 F.2d 1252, 1255 (C.C.P.A. 1977)).

In support of her statement regarding the osmolality of commercially available animal media, the Examiner cites Waymouth, Table 7. According to the Examiner:

> [I]t is known that initial osmola[l]ity of regular animal media or initial osmola[l]ity of the majority of commercially available animal media is within the claimed range of 280-320 mOsm (see table 7 of the reference by Waymouth [IDS-BG]). Thus, the cited methods are reasonably expected to inherently comprise the use of identical initial osmola[l]ity of the culture media as required for the presently claimed method. Office action, page 6.

Applicants respectfully submit that Waymouth fails to establish inherency because the allegedly inherent feature, that is, the starting osmolality of cell culture within the range recited in claim 1, does not necessarily flow from the teachings in Waymouth.

Table 7 of Waymouth shows the osmolalities of commercial and other tissue culture media. Waymouth, Table 7 at page 120. However, ***the starting osmolality of a medium is distinct from a starting osmolality of a cell culture***. "The expression "osmolality" is a measure of the osmotic pressure of dissolved solute particles in an aqueous solution. The solute particles include both ions and non-ionized molecules." Applicants' specification at page 7, lines 25 – 27. Further, ***there are many factors that can influence the starting osmolality of a cell culture.*** "Solutes which can be added to the culture medium so as to increase the osmolality thereof include proteins, peptides, amino acids, non-metabolized polymers, vitamins, ions, salts, sugars, metabolites, organic acids, lipids, etc." Applicants' specification at page 7, lines 29 - page 8, line 2. Therefore, a starting cell culture that can contain any number of different solutes/constituents can have a starting osmolality that is far different than the starting osmolality of only one of the constituents, namely the medium. ***In other words, the starting osmolality of a starting medium does not dictate the starting osmolality of an entire cell culture***.

Moreover, Waymouth teaches that a particular medium does not necessarily have a specific osmolality that is consistent with the results of the survey reported in Table 7. As admitted in Waymouth, "***[v]ariations between batches, and between samples of supposedly the same formulation from different suppliers, are wide. Variations between samples of a single medium (Eagle's Minimal Essential Medium) ranged from 288 to 820 mOsm***." Waymouth at page 119,

col. 2, par. 2 (emphasis added). Additionally, the reference admits, "[d]ifferences of this magnitude probably reflect differences in composition (e.g. use of hydrated or non-hydrated salts) and certainly must affect reproducibility of results in and between laboratories using these media without being aware of the differences." *Id.*

Applicants submit that Waymouth sheds no light on the osmolality of the particular batches of media employed by Glacken or in JP-1. Furthermore, the disclosure of a particular medium with an osmolality within the range recited in claim 1 would not be sufficient to establish that the starting osmolality of the cell culture would also be in the recited range.

Applicants respectfully submit that Glacken and JP-1, in light of Waymouth, fail to teach, expressly or inherently, each of the elements recited in claim 1. Thus, none of the above-cited references can support a *prima facie* case of anticipation.

35 U.S.C. §103(a).

Claims 1 and 20-25 were also rejected under 35 U.S.C. §103(a) as allegedly obvious over Glacken et al. [IDS-AT] or JP 1-101882 [IDS-AJ], in light of Waymouth [IDS-BG], taken with Kurano et al. [IDS-BK] (hereinafter "Kurano BK") and Kurano et al. [IDS-BJ] (hereinafter "Kurano BJ"). This rejection is respectfully traversed.

In order to make out a *prima facie* case of obviousness, the Examiner must demonstrate that the cited reference(s): (1) teach or suggest each element of the claimed invention; (2) provide motivation to those of ordinary skill in the art to combine or modify these elements to arrive at the claimed invention; and (3) reveal that, in making the claimed invention, those of ordinary skill in the art would have a reasonable expectation of success. See In re Vaeck, 947 F.2d 488 (Fed. Cir. 1991).

Applicants submit that the Examiner has not established a *prima facie* case of obviousness under section 103 because both Glacken and JP-1, in view of Waymouth, taken with Kurano BK and Kurano BJ, fail to teach or suggest the combination of elements of the claimed invention. In particular, the Examiner has identified no motivation to combine or modify the elements to arrive at the claimed invention. Further, one skilled in the art would not have a reasonable expectation of success in combining the teachings of the references.

The References Fail to Teach or Suggest the Recited Starting Osmolality and Control of Glucose Concentration

In explaining the rejection under section 103, the Examiner indicated that Glacken and JP-1 are relied upon for the reasons discussed in connection with the section 102 rejection. Office action page 7. Applicants submit that both Glacken and JP-1, in view of Waymouth, taken with Kurano BK and Kurano BJ, fail to teach or suggest the combination of elements recited in claim 1 of the present invention. In particular, the references fail to teach or suggest a method of growing animal cells in fed batch culture that includes "culturing the cells at a starting osmolality of about 280-330 mOsm" in combination with "controlling glucose concentration throughout the culturing to be at a concentration between about 0.02 and about 0.2 g/L, inclusive," and adding glucose to the cell culture as required to maintain said glucose concentration. As discussed above, both Glacken and JP-1 fail to teach or suggest a cell culture comprising culturing the cells at a starting osmolality of about 280-330 mOsm. As also discussed above, Glacken fails to teach or suggest controlling glucose concentration throughout the culturing to be at a concentration between about 0.02 and about 0.2 g/L, inclusive. Furthermore, Waymouth fails to cure the shortcomings of Glacken and JP-1 because Waymouth does not establish that the cell cultures described in these references had a starting osmolality within the range recited in the present invention.

The secondary references, Kurano BK and Kurano BJ, suffer from the same shortcomings as the primary references in that, the Kurano references neither teach nor suggest the recited combination of starting osmolality and control of glucose concentration.

The Examiner cites the summary of Kurano BK for teaching that the best growth of CHO cells is observed when the osmola[l]ity is about 320 mOsm. Office action, page 8. This passage of the reference describes how CHO cells were cultivated in a compact loop bioreactor and how the effects of physical and chemical environments upon the growth of suspended cells in the bioreactor were determined in batch cultures. Kurano BK, Summary at page 101. In Kurano BK, the effects of pH in the medium, stirring speed of impellers, temperature and partial pressure of oxygen upon growth of suspended cells, and an effect of medium osmolality were evaluated. *Id.*

Applicants respectfully submit that not only does Kurano BK fail to recognize the importance of a starting osmolality of about 280-330 mOsm, but the reference actually reports that ***"[i]t was obvious that no significant reduction in [specific growth rate] was found up to 390 mOsm kg^{-1} . . .."*** Kurano BK at page 107, par. 4 (emphasis added). As the reference further

indicates, " . . . up to 390 mOsmol kg^{-1} μ (specific growth rate) is not greatly influenced." Kurano BK at page 108, par. 2. Moreover, the reference clearly states, "[i]n the range between 320 and 390 mOsmol kg^{-1}, the results suggest that (1) there is no need to consider a physical effect of a substance when it is added to the medium in order to test a biochemical effect of it on CHO cells, [and] (2) ***increase in osmolality by base addition for pH control does not have a serious effect***." *Id.* (emphasis added).

Kurano BK also fails to teach or suggest culturing cells in the presence of glucose, controlled throughout the culturing to be at a concentration between about 0.02 and about 0.2 g/L, inclusive. Further, Kurano BK fails to teach or suggest adding glucose to the cell culture as required to maintain said glucose concentration. Therefore, the reference cannot teach or suggest the combination of elements recited in claim 1 of the present invention. To the contrary, in Kurano BK the evaluation of growth kinetics entailed monitoring glucose consumption and lactate formation pattern. See Kurano BK at page 108, par. 3. Therefore, glucose was not added to the cell culture as required to maintain the glucose concentration as recited in claim 1 of the present invention. Furthermore, the cell concentration was evaluated "[a]fter glucose had been depleted . . .." *Id.* Applicants respectfully submit, therefore, that Kurano BK fails to teach or suggest the combination of elements as recited in the present invention.

In explaining the rejection under section 103, the Examiner indicates that Kurano BJ teaches a maximum grow[th] rate of CHO cells at lowest glucose concentration of about 0.01- 0.25 g/L, citing Figure 3, and/or a maximum viable cell count at glucose concentration below about 0.5 g/L in fed batch, citing Figure 6. Office action, page 8. Figure 3 of Kurano BJ reflects dose inhibition of CHO cell growth by glucose. Kurano BJ, Figure 3 at page 118. Growth conditions were the same as Kurano BJ, Figure 1 where cells were grown in T-75 flasks at 37°C under 5% CO_2. *Id.* However, significantly, Figure 3 of Kurano BJ shows culture conditions in which glucose concentration was steadily increased from a concentration below 0.5 g/L up to about 2.0 g/L. *Id.* The reference also describes the effect of glucose concentration on the growth of CHO cells in the bioreactor with an initial glucose concentration of 1.15 that was increased to 2.74 and to 4.58 g/L. See Kurano BJ, Table 1 at page 117. Additionally, Kurano BJ, Figure 6B shows " [i]nitial glucose concentration was 0.64 g/L. It decreased until 0.35 g/L after 1d, then the glucose feed was started." Kurano BJ at page 124, par. 1. Therefore, Applicants respectfully submit that the reference clearly

fails to teach or suggest controlling glucose throughout the culturing to be at a concentration between about 0.02 and about 0.2 g/L, inclusive.

As with Glacken and JP-1, Kurano BJ also fails to teach or suggest culturing cells at a starting osmolality of about 280-330 mOsm. In Kurano BJ, an effect of lactate on the growth and/or product formation was examined. Kurano BJ at page 115, par. 5. The reference indicates that "at the highest lactate concentration . . . the osmolality was 370 mOsmol kg^{-1}. However, the reference is devoid of any teaching or suggestion of culturing the cells at a starting osmolality within the range recited in claim 1. Furthermore, the reference indicates, "***in a range of ammonia concentrations in Fig. 2, increase in osmolality can hardly affect the cell growth***." Kurano BJ at page 116, par. 3 (emphasis added).

Thus, the Kurano references fail to teach or suggest the specific combination of "***a starting osmolality of about 280-330 mOsm***" with "***glucose controlled throughout the culturing to be at a concentration between about 0.02 and about 0.2g/L, inclusive***." Accordingly, Applicants submit that the Kurano references do not remedy the deficiencies of Glacken and JP-1, in view of Waymouth, taken with Kurano BK and Kurano BJ.

The References Provide No Motivation for Combining the Recited Starting Osmolality and Control of Glucose Concentration

Applicants respectfully submit that the Examiner cannot pick and choose from among the teachings of, in this case, five different references to arrive at an approximation of Applicants' invention. Rather, to establish a *prima facie* case of obviousness, the Examiner must show that the cited references provide motivation to those of ordinary skill in the art to combine or modify these elements to arrive at the claimed invention. The teaching or suggestion to make the claimed combination . . . must be found in the prior art, and not based on the applicant's disclosure. In re Vaeck, 20 USPQ2d 1438 (Fed. Cir. 1991). In addition, the Examiner must consider the teachings of the references as a whole. The Examiner is not free to use the applicant's disclosure as a blueprint for the invention and disregard any teachings in the references that would tend to lead away from the invention. Finally, it is well-settled that "to establish obviousness based on a combination of the elements disclosed in the prior art, there must be some motivation, suggestion or teaching of the desirability of making the ***specific*** combination that was made by the applicant." *In Re Werner Kotzab*, 217 F.3d 1365; 2000 U.S. App. LEXIS 15504; 55 USPQ2d 1313 (Fed. Cir. 2000) (citations

omitted). The Federal Circuit has acknowledged that "the teaching, motivation or suggestion may be implicit from the prior art as a whole, rather than expressly stated in the references." *Id.* (citations omitted). But the Federal Circuit has unequivocally stated that:

> Whether the Board [or, in this case, the Examiner] relies on an express or an implicit showing, it must provide ***particular findings*** related thereto. See *Dembiczak, 175 F.3d at 999, 50 U.S.P.Q.2D (BNA) at 1617.* ***Broad conclusory statements standing alone are not "evidence."***

Id. Furthermore, the Werner court stated that "a rejection cannot be predicated on the mere identification in [the cited references] . . . of individual components of claimed limitations. Rather, ***particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed.***" *Id.* Applicants respectfully submit that this standard has not been met in the present case.

None of the references provide motivation to those skilled in the art to combine culturing cells at a starting osmolality of about 280-330 mOsm with controlling glucose throughout the culturing to be at a concentration between about 0.02 and about 0.2g/L. As stated above, Glacken fails to teach or suggest growing animal cells in fed batch cell culture comprising culturing the cells at a starting osmolality of about 280-330 mOsm. Glacken likewise does not teach or suggest making a determination of the starting osmolality of the cell culture. Further, Glacken fails to teach or suggest the importance of a particular starting osmolality for culturing cells, and also fails to teach or suggest monitoring and controlling factors in order to achieve a cell culture starting osmolality within the range recited in claim 1. Moreover, as discussed above, Glacken fails to teach or suggest controlling glucose throughout the culturing to be within the range recited in claim 1.

As also stated above, the JP-1 reference describes a perfusion system in which osmolality is not even measured or determined, and in which the importance of a starting osmolality of the cell culture is not taught or suggested. Therefore, JP-1 likewise fails to provide motivation to those of ordinary skill in the art to combine or modify the elements to arrive at the claimed invention.

Furthermore, neither Kurano BK nor Kurano BJ offer any teaching or suggestion to make the claimed combination. As stated, Kurano BK describes culturing conditions where the glucose concentration was depleted rather than controlled throughout the culturing within the range recited in Applicants' claim 1. See Kurano BK at page 108, par. 3. Additionally, Kurano BJ,

Figure 3 shows cell culture conditions wherein the glucose concentration is increased from 0.0. to 2.0 g/L. Hence, glucose concentration is not controlled throughout the culturing to be within the range recited in claim 1. Moreover, neither of the Kurano references indicate the importance of starting osmolality, much less provide motivation to use the specific range of 280-330 mOsm for the starting osmolality in combination with glucose concentration maintained throughout culturing in the specific range of 0.02 and about 0.2g/L.

Therefore, Applicants respectfully submit that none of the references provide the requisite ***specific*** motivation to those skilled in the art to combine "culturing cells at a starting osmolality of about 280-330 mOsm" with "controlling glucose throughout the culturing to be at a concentration between about 0.02 and about 0.2g/L by adding glucose to the cell culture as required to maintain said glucose concentration," as recited in claim 1.

↓ Ref. specifically teach 320 and low glucose for CHO cells.

No Reasonable Expectation of Success

Applicants respectfully submit that the Examiner has not established that one skilled in the art would have a reasonable expectation of success in combining the teachings of the references. Cell culture involves complex interactions among the myriad components in the culture which are influenced by a wide variety of culture conditions. As one skilled in the art readily appreciates, an observation that "good cell growth" is achieved by adjusting two components or conditions independently does not necessarily indicate that good cell growth will be achieved when the components or conditions are similarly adjusted simultaneously. At best, observations such as those reported in the cited references might arguably lead one skilled in the art to ***try*** a simultaneous adjustment of two or more parameters, but the record is devoid of any evidence that the results of such an experiment are predictable. The Examiner is respectfully reminded that the record must establish more than "obviousness to try" to make out a *prima facie* case of obviousness.

In summary, the primary references fail to teach or suggest the claimed invention, and the secondary references fail to cure the shortcomings of the primary references. In particular, the cited references, whether taken alone or in any combination, fail to teach or suggest the combination of the starting osmolality and the control of glucose concentration recited in claim 1. The record provides no evidence as to why the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed. Therefore,

Applicants submit that a *prima facie* case of obviousness has not been demonstrated. Applicants respectfully request that the rejection under section 103(a) be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believes all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (510) 337-7871.

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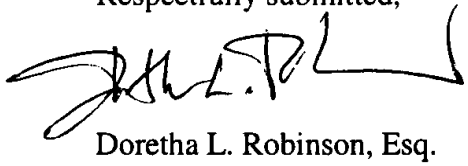
Respectfully submitted,



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APPENDIX A

CLAIMS PENDING IN USSN 09/661,161 WITH ENTRY OF THIS AMENDMENT

1. (Amended) A method of growing animal cells in fed batch cell culture comprising culturing the cells at a starting osmolality of about 280-330 mOsm in the presence of glucose controlled throughout the culturing to be at a concentration between about 0.02 and about 0.2 g/L, inclusive, by adding glucose to the cell culture as required to maintain said glucose concentration and thereby controlling osmolality of the cell culture.

20. The method of Claim 1 wherein the culture medium contains excess amino acids.

21. The method of Claim 1 wherein the initial cell seed density is between about 3×10^5 and about 1.5×10^6 cells/mL.

22. The method of Claim 1 wherein the cells are mammalian cells.

23. The method of Claim 22 wherein the cells are Chinese Hamster Ovary (CHO) cells.

24. The method of Claim 22 wherein the mammalian cells comprise a nucleic acid encoding a polypeptide.

25. The method of Claim 1 wherein the glucose control comprises flow injection analysis (FIA).